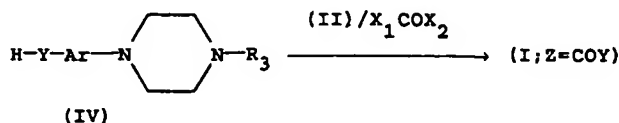


<p>98-390317/34 B03 FABR 97.01.15 FABRE MEDICAMENT SA PIERRE *FR 2758327-A1 97.01.15 97FR-000336 (98.07.17) C07D 401/12, A61K 31/495 (C07D 211:64, 295:155, 401/12) (C07D 211:52, 401/12, 295:15) (C07D 211:16, 401/12, 295:15) New piperidinyl-substituted N-aryl-piperazine derivatives - used as selective 5-HT-1D and 5-HT-1B receptor antagonists, e.g. for treating depression, anxiety or cancer C98-118101 Addnl. Data: HALAZY S, LAMOTHE M, JORAND L C</p>	<p>B(7-D5, 7-D11, 14-H1, 14-J1) .4</p>
<p>Piperidinyl-substituted N-aryl-piperazine derivatives of formula (I) and their hydrates, solvates and bio-precursors, including geometric and optical isomers and their mixtures (especially racemates), are new.</p> <div data-bbox="259 525 730 651"> <p style="text-align: center;">(I)</p> </div> <p>R₁ = R'₁, OR'₁, SR'₁, NHR'₁, COR'₁, CH(OH)R'₁ or CH₂R'₁;</p>	<p>R'₁ = Ar'; Ar' = phenyl, naphthyl or pyridinyl (all optionally substituted by one or more of 1-5C alkyl, halo, OH, OR₄, SR₄, CF₃, CH₂CF₃, NO₂, CN, COR₄, COOR₄, NHR₄, NHCOR₄, NHCOOR₄, NHSO₂R₄ and SO₂R₄); R₄ = H or 1-5C alkyl; R₂ = Cl, F, Br, OH, NH₂, CN, NO₂, R'₂, OR'₂, SR'₂, NHR'₂, COR'₂, CH(OH)R'₂, COOR'₂, NHCOR'₂, NHCOOR'₂, NHSO₂R'₂ or OCONHR'₂; R'₂ = 1-5C alkyl, Ar' or Ar'-alkyl; provided that if R₁ = OR'₁, SR'₁ or NHR'₁, then R₂ = R'₂, COOR'₂, COR'₂ or CH(OH)R'₂; Z = CO(CH₂)_nO, CO(CH₂)_nNH, (CH₂)_mO, (CH₂)_mNH, CO(CH₂)_pCONH, (CH₂)_pCONH, CO(CH₂)_pNHCONH, (CH₂)_pNHCONH, CO(CH₂)_pOCONH, (CH₂)_pOCONH, CO(CH₂)_pNHCOO or (CH₂)_pNHCOO; n = 0-8; m = 2-8; p = 1-8;</p> <p style="text-align: right;"> FR 2758327-A+</p>

<p>Ar = arylene such as phenylene or naphthylene, optionally substituted by one or more of 1-6C alkyl, 1-6C alkoxy and halo; R₃ = 1-6C alkyl.</p> <p>MORE SPECIFICALLY Ar = phenylene (optionally mono-substituted by OMe, Me or Cl in the ortho-position to the piperazinyl group); or naphthylene with the piperazinyl group in the 1-position and the -Z-piperidinyl group in the 7-position; R₃ = Me; Z = CO(CH₂)_nO, CO(CH₂)_nNH, (CH₂)_m or (CH₂)_mNH; R₁ = R'₁ or CH₂R'₁; R₂ = CN, OH, OR'₂, R'₂, NH₂ or NHR'₂.</p> <p>USE (I) are 5HT-1D and 5HT-1B receptor antagonists, and are useful for treating or preventing disorders associated with serotonin, e.g. CNS and cell proliferation disorders. They are especially used for treating or preventing depression, compulsive-obsessive disorders, anxiety, panic attacks, schizophrenia, aggression, bulimia, alcoholism, pain, neuro-degenerative diseases (e.g. Parkinson's and Alzheimer's disease) or cancer (all claimed).</p>	<p>Other disorders which may be treated include movement disorders, agoraphobia, memory disorders, dementia, amnesia, appetite disorders, sexual dysfunction, endocrine disorders (e.g. hyperprolactinaemia), vasospasm, hypertension and gastrointestinal disorders involving motility and secretion.</p> <p>Daily dose for adults is 0.001-1 (preferably 0.005-0.25) g, preferably orally. Claimed compositions containing (I) optionally also contain a further antidepressant active agent, especially milnacipran and/or a 5HT-1A antagonist.</p> <p>ADVANTAGE (I) are potent and selective antagonists of human 5HT-1D and 5HT-1B receptors, having especially high selectivity for such receptors relative to 5HT-1A, 5HT-1C, 5HT-2, α₁, α₂ and D₂ receptors.</p> <p>PREPARATION The following processes are claimed.</p> <p style="text-align: right;"> FR 2758327-A+/1</p>
---	--

<p>98-390317/34</p> <p>(a)</p> <div data-bbox="162 1596 730 1743"> <p style="text-align: center;">(II) + (III) → (I; Z=Z')</p> </div> <p>Q = L-Z'-; Z' = CO(CH₂)_nO, CO(CH₂)_nNH, CO(CH₂)_pCONH, CO(CH₂)_pNHCONH, CO(CH₂)_pOCONH or CO(CH₂)_pNHCOO,</p>	<p>provided that n is other than 0; L = OH, Cl or residue of an activated COOH group.</p> <p>(b)</p> <div data-bbox="893 1596 1380 1764"> <p style="text-align: center;">(II) + (III') → (I; Z=Z'')</p> <p style="text-align: center;">(in)organic base polar aprotic solvent</p> </div> <p>(III') = as for (III) but with Q = X-Z''-; Z'' = (CH₂)_mO, (CH₂)_mNH, (CH₂)_pCONH, (CH₂)_pNHCONH, (CH₂)_pOCONH or (CH₂)_pNHCOO;</p> <p style="text-align: right;"> FR 2758327-A+/2</p>
--	--

X = leaving group such as Cl, Br, I, tosyloxy, mesyloxy or OSO_2CF_3 .
(c)



Y = O or NH;

X₁, X₂ = leaving groups such as Cl or OCCl_3 .

EXAMPLE

A solution of 491 mg 4-methoxy-3-(4-methylpiperazin-1-yl)-aniline and 200 ml pyridine in 20 ml CH_2Cl_2 was treated under N_2 at 0°C with a solution of 240 mg triphosgene in 30 ml CH_2Cl_2 , stirred at room temperature for 30 minutes, treated with a solution of 413 mg 4-cyano-4-phenylpiperidine and 200 ml pyridine in 10 ml CH_2Cl_2 and stirred for 12 hours at room temperature. Work-up and

chromatographic purification gave 558 mg (61%) of (4-cyano-4-phenyl-piperidin-1-yl)-N-(4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl)-amide, which was converted into the fumarate by reaction with fumaric acid in methanol.

BIOLOGICAL DATA

(I) had IC_{50} values of 10-1,000 nM for inhibition of the sumatriptan-stimulated incorporation of labelled thymidine into C₆ type glial cells transfected with the 5HT-1D and 5HT-1B receptor genes. No specific values for individual compounds are given. (AB) (48pp2400DwgNo.0/0)

FR 2758327-A/3